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Unproven value of end-of-treatment and serial follow-up FDG-PET in primary mediastinal B-cell lymphoma

A recent study by Melani *et al.*[1] aimed to determine the value of end-of-treatment FDG-PET and serial follow-up FDG-PET in patients with primary mediastinal B-cell lymphoma (PMBCL) treated with dose-adjusted EPOCH-R. End-of-treatment FDG-PET was performed in 80 patients, 57 of whom received 144 serial follow-up FDG-PET scans. End-of-treatment FDG-PET scans were interpreted according to the Deauville criteria, with a score of 4 or 5 considered to indicate a positive result. After treatment, 55/80 (69%) patients had negative end-of-treatment FDG-PET results. With a median follow up of 8.4 years (range 1.8-18.4 years), only 1 relapse (1.8%) occurred in these 55 patients, therefore yielding a negative predictive value (NPV) of 98.2% for end-of-treatment FDG-PET. On the other hand, end-of-treatment FDG-PET was positive in 25 patients. Despite the very long follow-up period, only 5/25 (20%) with positive end-of-treatment FDG-PET results appeared to suffer from treatment failure. Of the 6 patients with treatment failure (one with negative and five with positive end-of-treatment FDG-PET), 4 underwent biopsies that confirmed the presence of residual lymphoma, whilst treatment failure was determined on the basis of serial follow-up imaging in 2 patients. One patient without biopsy confirmation showed progression on CT with an end-of-treatment maximum standard uptake value (SUV_{max}) of 14.5, and received salvage radiotherapy. The second patient without biopsy confirmation showed progression on treatment with increases in SUV_{max} from 10.2 to 21.3 and appearance of new lesions, and received radiotherapy. Four treatment failures were successfully salvaged with radiotherapy alone (n=2), resection alone (n=1), and chemotherapy/transplantation/radiotherapy (n=1). The other 2 patients with treatment failure died after unsuccessful administration of multiple salvage regimens. The investigators observed a decrease in SUV_{max} on serial follow-up FDG-PET scans in patients without disease relapse, compared to an increase in SUV_{max} in patients with treatment failure, and reported this to be a significant predictor of outcome in the regression analysis. Melani *et al.*[1] postulated a negative end-of-treatment FDG-PET result to be highly predictive of cure, whilst a single positive end-of-treatment FDG-PET scan does not accurately indicate treatment failure. In addition, they claimed that serial follow-up FDG-PET imaging effectively discriminates residual disease from post-treatment inflammatory changes, which may help to identify patients who require additional radiotherapy.

However, we disagree with their conclusions. Considering their claim that end-of-treatment FDG-PET has a high NPV for ruling out residual lymphoma, we believe that the low number of treatment failures in end-of-treatment FDG-PET negative patients may more likely be a reflection of the low incidence of disease relapse (6/80, 7.5%) rather than the discriminatory value of end-of-treatment FDG-PET. Even a diagnostic test without any discriminatory value at all (i.e., a test which would classify all patients as negative) would have a high NPV of 92.5% (74/80) in that scenario. Thus, FDG-PET had only minor additional value in that context. Note that the relapse rates were higher in other comparable studies, with relapse rates up to 9.4% in PMBCL patients with negative end-of-treatment FDG-PET results after immunochemotherapy who did not receive radiotherapy.[2-4] Of note, in diffuse large B-cell lymphoma (DLBCL), which has a considerably higher incidence of disease relapse than PMBCL, the NPV of end-of-treatment FDG-PET decreases enormously.[5-7] One study even reported that patients with high-risk DLBCL (as determined by the National Comprehensive Cancer Network International Prognostic index (NCCN-IPI) had a dismal progression-free survival of only 38.5% despite a negative end-of-treatment FDG-PET result.[7]

Furthermore, for several reasons we do not agree with Melani *et al.*[1] when they state that serial follow-up FDG-PET has value in discriminating patients with residual disease from those with therapeutic inflammation in order to decide which patients need additional radiotherapy. Firstly, we believe that as a result of the very low number of patients experiencing treatment failure (n=6) in their cohort, no clear conclusion can be drawn as to the value of serial follow-up FDG-PET in predicting treatment failure. Secondly, it should be mentioned that the study by Melani *et al.*[1] suffered from incorporation bias. Note that the value of the index test (serial follow-up FDG-PET) was determined using serial follow-up FDG-PET findings as reference standard in 2/6 cases of (presumed) treatment failure which were not confirmed by biopsy. Thirdly, of the 5 patients with treatment failure and positive end-of-treatment FDG-PET results, only 3 (60%) were successfully salvaged (2 with radiotherapy, and 1 with resection), whilst 2 died despite the application of multiple salvage regimens, indicating that (early) detection of treatment failure using multiple FDG-PET scans had no value in these patients in terms of a survival benefit. Of the 2 patients successfully treated with radiotherapy, it remains unknown whether the radiotherapy was actually successful in eradicating the lymphoma as histological evidence of residual disease was lacking and disease presence was only determined by means of serial follow-up FDG-PET findings. Note that multiple studies have shown that the application of routine follow-up FDG-PET examinations has no survival benefit in patients with negative end-of-treatment FDG-PET results.[8-10] Considering the very low incidence of treatment failure in PMBCL patients with positive end-of-treatment FDG-PET results, the lack of a survival benefit of routine follow-up imaging studies may also apply to this group of patients.

In conclusion, the high NPV of end-of-treatment FDG-PET in PMBCL remains unproven because the favorable prognosis of patients with negative end-of-treatment FDG-PET results may be a reflection of the generally good prognosis of patients with PMBCL rather than the value of end-of-treatment FDG-PET in ruling out residual lymphoma. Multiple studies in DLBCL have already revealed that end-of-treatment FDG-PET is unable to exclude residual lymphoma, with high proportions of patients developing disease relapse during follow up.[5] Finally, we believe that the value of serial follow-up FDG-PET in determining residual lymphoma remains unproven: the number of patients who experienced treatment failure was very low; the reference standard was inadequate and included serial follow-up FDG-PET findings resulting in incorporation bias; and there was a lack of proof that serial follow-up FDG-PET improves patient survival.

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